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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,764	LENZ ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,48,50,52-54 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,48,50,52-54 and 56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/10/2005 has been entered.

2. Currently, claims 47-48, 50, 52-54 and 56-67 are pending in the instant application. The amendments and arguments filed 11/10/2005 have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The response filed 11/10/2005 appears to erroneously indicate that claims 47-49, 51-54, and 56-67 are pending, however the amendment filed 11/10/2005 canceled claims 49, 51, and 55. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow, where appropriate. This action is Non-Final.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The rejection of claims under 35 USC 102(b) made in sections 9, 10, and 11 of the previous office action are withdrawn in view of the amendments to claim 47.

5. The rejection of claims 47-67 under 35 USC 112/2nd paragraph made at section 8 of the previous office previous office action is withdrawn in view of the amendments to claim 47.

Claim Rejections - 35 USC § 112

Written Description

6. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

Claim 67 recites "wherein the subject suffers from a cancer selected from ... liver cancer". A thorough review of the specification and the originally filed claims fails to provide support for the broad recitation of liver cancer. Liver cancer encompasses, for example, HCC. While the specification teaches analysis of metastatic liver tumor sample in colorectal cancer patients, such recitation does not provide support for any liver cancer, including primary liver tumors. Accordingly, the specification as originally filed does not to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Indefinite

7. Claims 57-60, 61, 63, and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites "means for determining a genomic polymorphism", however the function of 'determining a genomic polymorphism' is vague because it can include a number of

different functions: such as amplifying, detecting sizes on a gel, etc. and it cannot be determined what specific function the "means" is drawn to.

Claim 57 recites "if present" which is vague and indefinite because it is not clear what the components of the kit would be if the polymorphism were not present. It is not clear if the recitation of "if present" is meant to indicate an alteration in the components of the kit depending on the presence or absence of the polymorphism in a sample.

Claim 61 lacks antecedent basis for the term "the subject's biological sample fluid" as there is no previous recitation to a biological sample *fluid.*

Claim 63 is indefinite as it contains Markush language "selected from the group consisting of", however there is no group set forth in the claim. The claim is only directed to peripheral blood cells. It is unclear if the term is meant to signify a single cell from a group of cells?

Claim 66 lacks antecedent basis for the term "the extratumoral cells" as there is no recitation of "extratumoral cells" in claim 66, 61-65, or 47.

Claim Rejections - 35 USC § 102

8. Claim 57 is rejected under 35 USC 102(b) as being anticipated by New England Biolabs catalog (1996, page 102).

New England Biolabs teaches a kit which contains a DNA ladder X174 DNA-Hae III Digest which contains base pairs on the order of 1,353 base pairs to 72 base pairs. Alternatively, New England Biolabs teaches a kit which contains a DNA ladder pBR322 DNA-BstN I Digest which contains base pairs on the order of 1, 857 to 13 base pairs (see page 102). Either of these

DNA ladders could be used as sequencing markers and appear to be a component of the kit of claim 58. Additionally, the DNA ladder is provided in a solution of 10 mM Tris and 1mM EDTA (claim 59). It is noted that the use for the kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..."

Response to Arguments

9. The response asserts that the kit contains a means for determining a genomic polymorphism of the 5' UTR of the TS gene and that nothing in the Biolabs indicate that the markers would specifically recognize a genomic polymorphism of the 5' UTR of the TS gene. This argument has been thoroughly reviewed but was not found persuasive. The specification sets forth a number of different methods for determining genomic polymorphisms: electrophoresis, automated sequencing, allele specific probes, differential restriction digestion, ligase mediated detection, "and the like". Accordingly, the "means" for determining the polymorphism appear to be very broad. Further, the specification exemplifies a method which used PCR amplification and size determination using gel electrophoresis (Fig. 1, page 14) which includes sequencing markers. The ladders taught by New England Biolabs can be used as size markers. For these reasons and the reasons already made of record, the rejection is maintained.

10. Claims 57-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Promega Catalog (1997), page 78.

Promega catalog teaches a kit comprising Taq DNA polymerase (means for determining a genomic polymorphism at a tandemly repeated 28 base pair sequence of the 5' UTR of the TS gene; claim 57), dNTPs, storage buffer, and reaction buffer (reagents, components provided in solution or as a liquid dispersion, claims 58-59).). It is noted that the use for the claimed kit and the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product...".

Claim Rejections - 35 USC § 103

11. Claims 57-60 are rejected under 35 USC 103(a) as being unpatentable over Horie in view Erlich (US Patent 5,468,613) and New England biolabs.

The Horie teaches a method for analyzing the number of repeats in the 5' UTR of the TS gene using PCR and size analysis on a gel (see page 192, col. 2-page 193; Figure 3). With regard to claim 57, the primers are considered means for determining a genomic polymorphism in the TS 5' UTR. It is further noted that the first primer taught by Horie is identical to instant SEQ ID NO: 6, and the 2nd primer of Horie "comprises" instant SEQ ID NO: 7 (contains 9 additional nucleotides on the 5' end), which are the primers the specification teaches were used

to "determine" the presence of the TS polymorphism. With regard to claims 58 ad 59, Horie teaches using Taq polymerase, dNTPs, and reaction buffer for the PCR reaction, and further teaches analysis on a 4% agarose gel, the use of molecular markers for size analysis, as well as DNA tandemly repeated sequences (claim 60). Horie does not teach packaging these means and reagents in kit format, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40) and further, Erlich teaches providing kits which include reagents for identifying alleles in hybridization assay. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie, for determining the TS 5' UTR repeat alleles of a subject, in kit format, for the obvious improvement of providing the reagents in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie more convenient to perform. It would have been further obvious to provide either size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that the use for the kit and the instructions in the kit carry no patentable weight. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

12. Claims 47-48, 52-54, 56, 64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano,

Horie teaches that triple tandemly repeated sequences are known to exist in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene and that the number of tandemly repeated sequences was found to be polymorphic among individuals (see abstract, and page 191, 2nd column). Horie teaches that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat (see abstract). Horie teaches detection in leukocytes (blood cells; claim 64) using PCR amplification surrounding the repeat region and determination of the size of amplicons to determine the repeat(s) present (pages 192-193). While Horie teaches that possible mechanisms for expression could occur at either the transcriptional or post transcriptional level, Horie teaches that the unique repeated structure is associated with either possibility (see page 195 column 2, to page 196, column 1, 2nd para). Horie does not teach a correlation between expression of the TS gene and sensitivity to chemotherapeutic drugs, however, Leichman et al disclose a method for determining the suitability of treating cancer in a subject with a chemotherapeutic drug (5-fluorouracil, 5-FU) by taking a biological sample of a subject and determining expression of the TS gene (see page 3224, page 3226 last para). Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU in the subjects. Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare

toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Ruano teaches that genetic variability is a determinant of a patient's response to therapy. Ruano teaches that by correlating a haplotype with disease and by using genome anthologies, which are collections of a specific locus, as targets for drug screening and development, it is possible to create a prognostic test for customizing therapy based on a patient's genotype (see column 7, lines 3-15). Further, Ruano teaches that different gene variants may be correlated to variable expression levels and that genome anthologies may comprise collections of regulatory sequences (see col. 12, lines 40-42).

Although Leichman does not teach that the expression of TS is correlated to a particular genotype, given the teachings of Horie, in view of Ruano, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at a method of screening a subject for sensitivity to 5-FU by determining the number of repeats in the 5' regulatory region (genotype) in each allele of the TS gene for the purposes of developing a genotypic assay for determining a subject's response to TS directed chemotherapy drugs. The ordinary artisan would have been motivated to determine if chemotherapy with 5-FU for patients with colorectal cancer could be customized for patients according to their genotype, that is the number of TS repeats, because Ruano teaches to create a prognostic test for customizing therapy based on a patient's genotype. Further, Leichman also provides motivation for screening as Leichman teaches that if patients with tumor sensitivity to 5-FU can be identified before the initiation of therapy, 5-FU based treatment could be targeted to that group and would spare

toxicity to patients unlikely to respond and would allow faster progress in new drug development.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), and 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

13. Claims 61-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of, in the alternative, Govindarajan or Howells.

The teachings of Horie and Leichman in view of Ruano are set forth above. Horie and Leichman in view of Ruano do not specifically teach to use peripheral blood cells (blood cells, claim 64) for TS allele detection

Howells teaches a method of correlating GSTT1 null and GSTM1 null genotypes to unresponsiveness to primary chemotherapy in patients with epithelial ovarian cancer. Howells teaches genotyping for the null alleles using PCR on DNA isolated from blood or tissue identified as macroscopically normal by the surgeon for genotyping (see abstract, p. 2440, col. 2, 4th para). Howells teaches that null alleles for both GSTT1 and GSTM1 was associated with nonresponsiveness to chemotherapy (see abstract, page 2443, col. 1, first para).

Govindarajan teaches a method using PCR to genotype the GSTM1 gene from peripheral blood cells in patients with lung cancer who had received 3 cycles of platinum based chemotherapy. Govindarajan teaches that there was a higher incidence of GSTM1 null genotypic expression in patients with SC responders (small cell cancer) as opposed to NSC responders (non small cell).

Both Howells and Govindarajan provide examples of methods for screening for sensitivity to chemotherapeutic drugs involving determining the genotype of a pre-selected gene from normal blood samples and correlating gene expression to sensitivity to the chemotherapeutic drug.

Although Leichman teaches detecting TS expression from tumor biopsies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine TS genotype from a subject's peripheral blood, for example, as taught by Govindarajan and Howells, because such method of genotype analysis is less invasive, less painful, and therefore obviously more preferable to the patient, than determining TS genotype from a biopsy. Horie teaches that the number of repeats is associated with TS expression in

normal cells, therefore the teachings of Horie provide a reasonable expectation of success that accurate TS genotype analysis can obtained for a subject from normal cells.

Given that Leichman teaches that expression levels of TS correlated with sensitivity to 5-FU and that Horie teaches that 1) TS expression is associated to the number of tandemly repeated sequences in the 5' terminal regulatory region of the human TS (thymidylate synthase) gene, 2) that the number of tandemly repeated sequences (genotype) was found to be polymorphic among individuals (see abstract, and page 191, 2nd column), 3) that the number of repeated sequences was found to result in differences in expression activity of the gene, with the double repeat showing lower expression than the triple repeat, , and 4) TS genotype could be determined for a subject from normal cells, it would have been prima facie obvious to the ordinary artisan at the time the invention was made to screen for a subject's sensitivity to 5-FU by determining the genotype of the number of tandemly repeated sequences in the 5' terminal regulatory region of the TS gene obtained from a subject's biological sample for the purpose of providing a genotypic assay which could be used as a prognostic indicator of response to 5-FU therapy in patients with colorectal cancer.

Response to Arguments

14. The response asserts that Horie identifies a TS polymorphism in the 5'UTR of the TS gene, but that neither Horie nor any of the secondary or tertiary references correlate this polymorphism to therapeutic effect or pathology, and that at best, they only provide an invitation to experiment. The response further asserts that Horie teaches away by stating that the polymorphism in the 5' terminal region is found in normal individuals and that the polymorphism might not be related to any abnormal physical condition. This argument as been

thoroughly reviewed but was not found persuasive. The rejection was not made over the teachings of Horie alone. In evaluating the *prior art as a whole*, the ordinary artisan would be led to the teachings of Leichman expression levels of TS correlated with sensitivity to 5'FU in subjects. While Horie teaches that "there are no data to suggest that the polymorphism *might* be related to any abnormal physical condition", Horie does not teach that it is not associated with abnormal physical condition. Horie teaches that the polymorphism is associated with altered expression activity of the gene and Leichman teaches that expression levels of TS correlated with sensitivity to 5'FU in subjects. Therefore, the rejection did not only set forth an invitation to experiment, as is asserted in the response.

15. Claims 57-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horie and Leichman in view of Ruano, as applied to claims 47-48, 52-54, 56, 64, and 67 above, and further in view of Erlich (US Patent 5,468,613) and New England biolabs.

The teachings of Horie and Leichman in view of Ruano are set forth above. Horie & Leichman, in view of Ruano, do not teach a kit comprising means for determining TS 5'UTR genotype or DNA tandemly repeated sequence of the TS gene, however Erlich teaches constructing allele specific probes for the purposes of identifying specific alleles in hybridization assays (see abstract, col. 5, lines 32-40). Further, Erlich teaches providing kits which include such sequence specific oligonucleotides. . Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the reagents taught by Horie for use in the method of Horie and Leichman in view of Ruano, for determining the TS 5' UTR repeat alleles of a subject, in kit format, for the obvious improvement of providing the

reagents in ready to use form, to make the method of detecting the repeats easier and more convenient to perform. The ordinary artisan would have been motivated to provide such an oligonucleotide in kit format for the obvious improvement of provided pre-weighed, premeasured reagents that would make the method of Horie and Leichman in view of Ruano more convenient to perform. It would have been further obvious to provide size markers, or the sequences of the different tandemly repeated alleles as positive controls in order to provide a comparison to determine the identity of the alleles detected, and to provide such nucleic acids in a solution of TE buffer as such was commonly used as a nucleic acid storage solution at the time of the invention, as evidenced by New England Biolabs catalog. It is noted that the use for the kit and the instructions in the kit carry no patentable weight. It is further noted that the temperature of the buffer solution carries no patentable weight as it does not provide any structural limitation to the kit.

Response to Arguments

The response's assertion that claims are directed to a kit for use in screening for the effectiveness of TS directed drug therapy and include means for determining the polymorphism and instructions for correlating the polymorphism of the 5'UTR of the TS gene with TS directed therapy are not found persuasive because the use for a kit carries no patentable weight. The kit of Horie and Leichman in view of Ruano and further in view of Erlich and New England biolabs contains means for determining the 28 base pair repeat polymorphism of TS gene 5'UTR for the reasons set forth above. Further, the instructions for the kit carry no patentable weight as they merely set forth an intended use for the components of the kit. Additionally, the components of the kit could be used for other processes and their use is not dependent on the instructions of the

kit. See In re Ngai, 03-1524 (CAFC 2004). The court held that "Here, the printed matter in no way depends on the kit and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product..."

Conclusion

16. No claims are allowable over the cited prior art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

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1/23/06